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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,912	05/09/2006	Keiichirou Kai	1034232-000038	4449

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EXAMINER	
BLAND, LAYLA D	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
11/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/578,912	KAI ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is a response to Applicant's amendment submitted August 26, 2009, wherein claim 1 is amended and claim 5 is canceled.

Claims 1, 4, and 6 are pending and are examined on the merits herein.

The following modified rejection was necessitated by Applicant's amendment submitted August 29, 2009, wherein claim 1 was limited to a phosphate donor:pentose ratio of 1:3 - 1:7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al. (Org. Biomol. Chem., 2003, 1, 2833-2839, July 9, 2003, of record) in view of Asano et al. (Journal of Molecular Catalysis B: Enzymatic 7 (1999) 271-277, PTO-1449 submitted December 8, 2008), and Gross et al. (J. Am. Chem. Soc. 1983, 105, 7428-7435, of record).

Tanaka et al. teach the phosphorylation of inosine to inosine-5'-monophosphate by nonspecific acid phosphatases from *Shigella flexneri* [page 2834, second paragraph]. The enzyme also mediates the phosphorylation of glucose to glucose-6-

phosphate using pyrophosphate as the phosphate donor [page 2835, last paragraph]. The specific activity of acid phosphatase derived from *Sh. flexneri* was 40 U mg^{-1} [page 2834, first paragraph]. In the enzymatic phosphorylation of inosine, 40mM inosine, 100mM disodium pyrophosphate, and 0.1-1μM of enzyme solution in a total volume of 1 ml was used [page 2838, last paragraph]. The amount of 5'-IMP increased with increasing PPi concentration [page 2834, Figure 2]. For the glucose phosphorylation, the reaction mixture contained 1μM PhoN, 100mM glucose and 100mM disodium pyrophosphate in 100mM sodium acetate [page 2839, first paragraph]. The classical chemical introduction of a phosphate group into a polyhydroxy compound is tedious, and since such structurally different compounds as glucose and inosine are able to enter the active site of the enzyme and were successfully phosphporylated, this method has potential as an alternative to chemical methods [page 2837, paragraph bridging the first and second column].

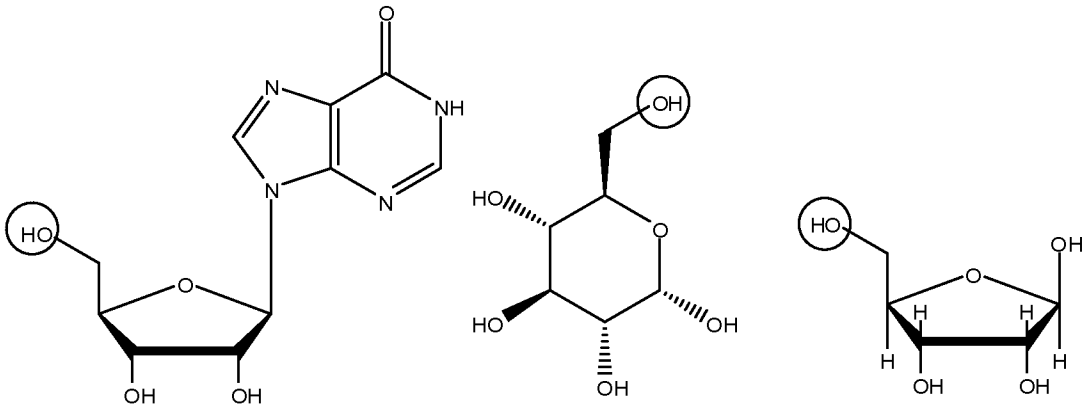
Tanaka et al. do not teach the phosphorylation of a free pentose and teach a 2.5:1 ratio of phosphate donor:pentose, not 3:1 to 7:1.

Asano teaches the enzymatic phosphorylation of inosine at the 5'-position. Reactions were carried out using 20 mg of inosine and 100 mg of tetrasodium pyrophosphate decahydrate [page 274, Table 1]. Considering that inosine has a molecular weight of about 268 and tetrasodium pyrophosphate decahydrate has a molecular weight of about 265, that corresponds to a molar ratio of about 376:75, or about 5:1.

Gross et al. teach that ribose 5-phosphate is an intermediate in the synthesis of nucleotides, histadine and tryptophan [page 7428, first paragraph]. Methods for preparing ribose 5-phosphate include obtaining the compound include chemical synthesis and enzyme-catalyzed synthesis using ribokinase [page 7429, Ribose 5-Phosphate].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a pentose-5-phosphate ester using acid phosphatase from *Shigella flexneri* in the presence of pyrophosphate. Tanaka teaches the selective phosphorylation of inosine (a nucleoside derived from a pentose) and glucose (a hexose). Tanaka teaches a donor:pentose ratio of about 2.5:1, but also teaches that higher concentrations of phosphate donor lead to higher yields of the product. Asana teaches donor:pentose ratio of about 5:1 for screening enzymes for enzymatic phosphorylation of nucleosides, so the skilled artisan would be led to choose a similar ratio. The skilled artisan would expect the corresponding reaction to proceed on a pentose in a substantially same or similar fashion because the structure of a pentose such as ribose is very similar to the structures of inosine and glucose with respect to the reaction sites, seen circled below. Further, Tanaka et al. teach that the enzyme is non-specific, and speculate that because it was effective for phosphorylation of inosine and glucose, that it might be widely applicable. The skilled artisan would have been motivated to prepare a pentose-5-phosphate ester because such compounds are useful intermediates in nucleotide synthesis, as taught by Gross et al., and are synthesized via

chemical methods which Tanaka et al. teach can be replaced by methods utilizing acid phosphatase.



Response to Arguments

Applicant argues that substrate specificity of an enzyme is highly unpredictable. This argument is not persuasive because the enzyme used by Tanaka et al. is a nonspecific acid phosphatase, and Tanaka et al. suggest that, because the reaction was effective for substrates of very different structures, the reaction might have broader utility. Furthermore, as set forth above, the reactive sites of inosine, glucose, and ribose are all very similar.

Applicant argues that reaction of deoxyribose under Tanaka's conditions for glucose results in poor yields, and thus a one-carbon difference in ring size can change the yield of the reaction. This argument is not persuasive because Tanaka teaches a higher concentration of pyrophosphate for phosphorylation of inosine than for glucose,

and also teaches that the yield depends on the concentration of pyrophosphate. Thus, the skilled artisan would expect that using a small amount of pyrophosphate would result in lower yields.

Applicant argues that Ishikawa et al. teach that the presence of a hypoxanthine is important for recognition of inosine as a substrate for the reaction of an acid phosphatase. On the contrary, Ishikawa et al. (PTO-1449 submitted April 4, 2008) teach that "there is little interaction between the enzyme and the inosine base." (see page 542, first column) Further, it is known that the reaction proceeds on glucose, which lacks a hypoxanthine.

Applicant argues that Ishikawa (US 6,987,008) teaches that an enzyme would be expected to recognize a nucleoside base, and that certain modifications to the enzyme which were designed to improve recognition of the nucleoside base resulted in improved activity. This argument is not persuasive because Tanaka teaches the phosphorylation of glucose, which has no nucleoside base. Thus, even if the enzyme is able to recognize a nucleoside base, a nucleoside base is clearly not required for activity. Furthermore, Ishikawa (previously addressed) teaches that the unmodified enzyme, wherein "there is little interaction between the enzyme and the inosine base," was also active. Thus, the inosine base is not required for activity.

Applicant's argument regarding the similarities between the enzymes from *Escherichia blattae* and *Shigella flexneri* are acknowledged. Thus, the skilled artisan would consider that if "there is little interaction between the enzyme and the inosine

base" as taught by Ishikawa when the enzyme from *Escherichia blattae* is used, the same would be true when the enzyme from *Shigella flexneri* is used.

Applicant argues that pentoses consist of equilibrium mixtures of furanose and pyranose, and that the pyranose could not be phosphorylated because it lacks a primary alcohol. This argument is not persuasive because the furanose, also present, has a primary alcohol and does react, as illustrated by Tanaka et al.

Applicant argues that some pentoses and hexoses are phosphorylated using acid phosphatase, and some are not, and presents the declaration of Keiichirou Kai in support. The declaration provides evidence that, of 7 pentoses, 2 did not react; and of 8 hexoses, 3 did not react. This argument is not sufficient because a ribose derivative has already been shown to react, and the evidence in the prior art shows that the base is not required, as there is “little interaction” between it and the enzyme and a free hexose also reacts. Thus, the skilled artisan would have a reasonable expectation that ribose would react. "Obviousness does not require absolute predictability of success." *Id*. at 903, 7”USPQ2d at 1681.

Applicant argues that the position of phosphorylated hydroxyl groups differ based on the acid phosphatase which is used, and that the skilled artisan would not expect selective phosphorylation at position 5 using *Shigella flexneri or Escherichia blattae*. This argument is not persuasive because Tanaka teaches that more 5’-IMP is produced compared to 3’-IMP [see Figure 2]. Furthermore, Asano’s reaction using *E. blattae* resulted in a ratio of 5’-IMP:3’-IMP of 100:0.2. Thus, the skilled artisan would expect

selectivity for the 5-position using Tanaka's acid phosphatase or Asano's *E. blattae*. It is noted that the claims do not require any particular acid phosphatase.

Applicant argues that Tanaka teaches 2.5 fold PPi to inosine by mole, not 3-7. This argument is not persuasive because Tanaka also teaches that increasing the concentration of PPi results in an increased yield. Furthermore, Asano teaches a much broader range of ratios which can be used, and exemplifies 5:1 for screening enzymes. Thus, the skilled artisan could envision that a higher concentration than Tanaka used would be effective, because Tanaka suggests using high concentrations of PPi. The skilled artisan could also look to Asano for guidance, and 5:1 is exemplified by Asano. Thus, the skilled artisan could envision using a ratio of about 5:1, and would have a reasonable expectation of success because that concentration worked for Asano.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Bland/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
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